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(54) Title: **DRUGS FOR CHRONIC PAINS**

(57) Abstract: Nitro-oxyderivative compounds or salts thereof having the following general formula (I): $A-(B)_{b0}-(C)_{c0}-NO_2$ wherein: c_0 is an integer and is 0 or 1, b_0 is an integer and is 0 or 1, $A = R-T_1$, wherein R is the radical of an analgesic drug for the chronic pain, in particular for the neuropathic pain; B is such that its precursor is selected from aminoacids, hydroxyacids, polyalcohols, compounds containing at least one acid function; C is a bivalent radical containing an aliphatic, heterocyclic or aromatic radical.

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DRUGS FOR CHRONIC PAINS

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The present invention relates to compounds having an improved efficacy in the reduction of the chronic pain, specifically the neuropathic pain.

For the description of the chronic pain, for simplicity, reference is made, from now on, to the neuropathic pain.

It is known that the neuropathic pain is a form of chronic pain originated from a damage or from a disease of the central or peripheral nervous system. The neuropathic pain comprises a series of painful symptomatology, such for example the following: the diabetic neuropathic pain, the painful post-infarct syndrome, the pain caused by the chemotherapeutic treatment, or it can derive from an infection caused by viral agents, such for example herpes, for instance Herpes zoster, etc.

The neuropathic pain generally afflicts the patients for years since the therapies with conventional analgesic drugs are not effective. Furthermore it is a social problem since the neuropathic pain besides the physical trouble causes in the patients a serious psychological stress.

In the last twenty years the research on the pathogenesis of the neuropathic pain has achieved significant progress. Studies carried out on human and animal experimental models of neuropathic pain, have shown that the central nervous system reacts to the algogen stimuli with a series of biochemical and physiopathological responses. This capability of the nervous system to functionally and morphologically adapt itself with algogen stimuli, is known

as neuroplasticity and it has an essential role in inducing the onset or in maintaining the painful symptomatology.

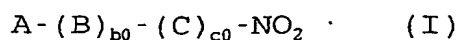
Among the drugs used in the neuropathic pain treatment the carbamazepine has been widely used in clinical studies, and the results obtained have shown the efficacy of said drug in the treatment of trigeminal neuralgia, of the diabetic neuropathic pain and in the post-herpetic neuralgia. However the administration of this drug produces in patients marked side effects such as for example, somnolence, dizziness, ataxy, nausea and vomit, which limit the use thereof.

In these last years other drugs for the treatment of the neuropathic pain have been experimented. Among these, it is in particular mentioned gabapentin, which has a high analgesic efficacy for the neuropathic pain treatment, particularly the diabetic neuropathic pain and the post-herpetic pain. However the therapy with gabapentin causes side effects of central type such as somnolence, weariness, obesity, etc. (Martindale XXXth Ed. p.374).

The need was therefore felt to have available drugs having in the treatment of the chronic pain, in particular neuropathic pain, an improved pharmacotherapeutic profile and/or lower side effects.

It has now been surprisingly and unexpectedly found that this technical problem can be solved with the class of drugs which is described hereunder.

An object of the present invention are nitrooxyderivative compounds or salts thereof having the following general formula (I):



wherein:

c_0 is an integer and is 0 or 1, preferably 1;

b_0 is an integer and is 0 or 1, with the proviso that c_0 and b_0 cannot be contemporaneously equal to zero;

$A = R-T_1-$, wherein R is the radical of an antipain drug for the chronic pain, in particular for the neuropathic pain;

$T_1 = (CO)_t$ or $(X)_{t'}$, wherein $X = O, S, NR_{1c}, R_{1c}$ is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, t and t' are integers and equal to zero or 1, with the proviso that $t = 1$ when $t' = 0$; $t = 0$ when $t' = 1$;

$B = -T_B-X_2-T_{BI}-$ wherein

T_B and T_{BI} are equal or different;

$T_B = (CO)$ when $t = 0$, $T_B = X$ when $t' = 0$, X being as above;

$T_{BI} = (CO)_{tx}$ or $(X)_{txx}$, wherein tx and txx have the value of 0 or 1; with the proviso that $tx = 1$ when $txx = 0$; and $tx = 0$ when $txx = 1$; X is as above;

X_2 , bivalent radical, is such that the corresponding precursor of $B -T_B-X_2-T_{BI}-$ wherein the free valences of T_B and of T_{BI} are saturated each with OZ, with Z or with

$-N(Z^I)(Z^{II})$, being:

$Z = H, C_1-C_{10}$, preferably C_1-C_5 alkyl linear or branched when possible,

Z^I, Z^{II} equal to or different have the values of Z as above, depending on that T_B and/or $T_{BI} = CO$ or X, in function of the values of t, t', tx and txx ;

the precursor compound of B as above defined is preferably selected from the following classes of compounds:

aminoacids, selected from the following: L-carnosine, anserine, selenocysteine, selenomethionine, penicillamine, N-acetylpenicillamine, cysteine, N-acetylcysteine,

glutathione or esters thereof, preferably ethyl or isopropyl ester;

hydroxyacids, selected from the following: gallic acid, ferulic acid, gentisic acid, citric acid, caffeic, dihydrocaffeic acid, p-cumaric acid, vanillic acid;

aromatic and heterocyclic polyalcohols, selected from the following: nordihydroguaiaretic acid, quercetin, catechin, kaempferol, sulfurethyne, ascorbic acid, isoascorbic acid, hydroquinone, gossypol, reductic acid, methoxyhydroquinone, hydroxyhydroquinone, propyl gallate, saccharose, 3,5-di-tertbutyl-4-hydroxybenzylthio glycolate, p-cumaric alcohol, 4-hydroxyphenylethylalcohol, coniferyl alcohol, allopurinol;

compounds containing at least one free acid function, selected from the following: 3,3'-thiodipropionic acid, fumaric acid, dihydroxymaleic acid, edetic acid;

C = bivalent radical $-T_c-Y-$ wherein

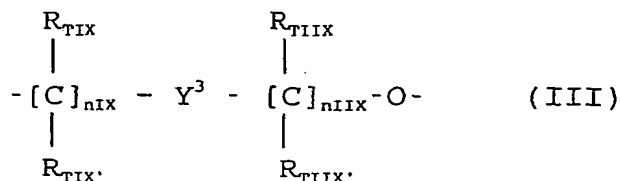
when $b_0 = c_0 = 1$: $T_c = (CO)$ when $tx = 0$, $T_c = X$ when $txx = 0$, X being as above defined,

when $b_0 = 0$: $T_c = (CO)$ when $t = 0$, $T_c = X$ when $t' = 0$, X being as above defined,

when $c_0 = 0$: $tx = 0$, $T_{BI} = X = -O-$;

Y has one of the following meanings:

Y_p :



wherein:

nIX is an integer from 0 to 5, preferably 1;

nIIX is an integer from 1 to 5 preferably 1;

R_{TIX}, R_{TIX'}, R_{TIIX}, R_{TIIX'}, equal to or different from each other are H or linear or branched C₁-C₄ alkyl; preferably

$$R_{TIX}, R_{TIX'}, R_{TIIIX}, R_{TIIIX'}, \text{ are } H;$$

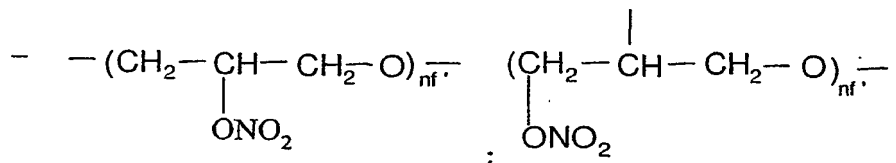
Y³ is a saturated, unsaturated or aromatic heterocyclic ring having 5 or 6 atoms, containing from one to three heteroatoms, preferably from one to two, said heteroatoms being equal or different and selected from nitrogen, oxygen, sulphur;

or Y can be:

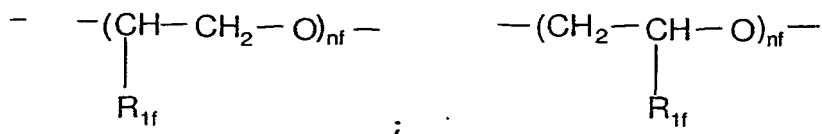
Y_0 , selected from the following:

an alkyleneoxy group R'O wherein R' is a linear or branched when possible C₁-C₂₀, having preferably from 2 to 6 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be substituted by heteroatoms, the ring can have side chains of R' type, R' being as above;

or Y is selected from one of the following groups:

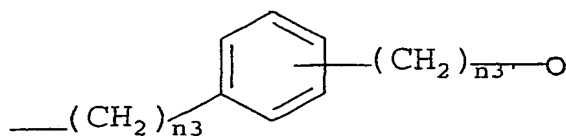


wherein nf' is an integer from 1 to 6 preferably from 1 to 4;



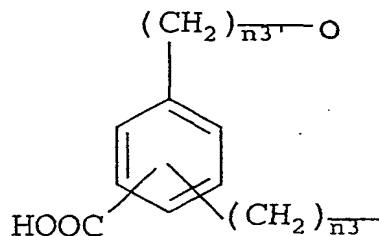
wherein $R_{1f} = H, CH_3$ and nf is an integer from 1 to 6; preferably from 2 to 4;

Y_{AR} , selected from:

Y_{AR1}:

(V)

wherein n_3 is an integer from 0 to 5 and n_3' is an integer from 1 to 3; or

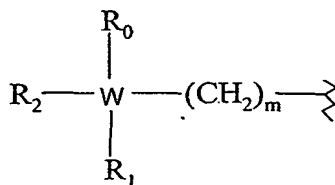
Y_{AR2}:

(VI)

wherein n_3 and n_3' have the above meaning.

The radical R in formula (I) is preferably that of chronic analgesic drugs, in particular of drugs for the neuropathic pain, and it can be selected from the conventional compounds used for these applications. Tricyclic antidepressive drugs and antiepileptic drugs can be mentioned.

Preferably R is the radical of an analgesic drug, having formula II:



(II)

wherein:

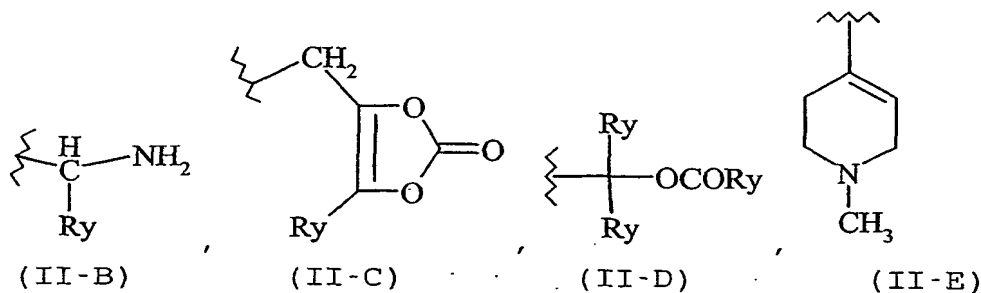
W is a carbon atom or a nitrogen atom;

m is an integer from 0 to 2;

$R_0 = H, -(CH_2)_n-NHR_{1A}$, n being an integer from 0 to 2, wherein

$R_{1A} = H, -C(O)-R_{1H}, -C(O)O-R_{1H}$, wherein

R_{1H} is a linear or branched C_1-C_{10} alkyl, a phenyl or benzyl group; or R_{1H} has one of the following meanings:



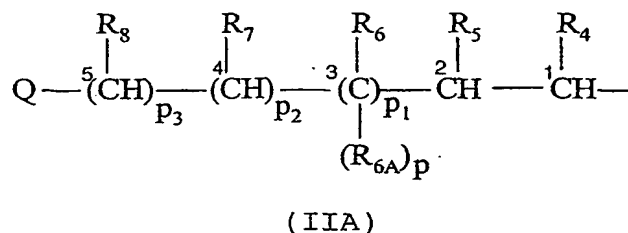
wherein R_y is hydrogen, a linear or branched C_1-C_{10} alkyl, a phenyl or benzyl group;

$R_1 = H$, when $W = N$, R_1 is the electronic doublet on the nitrogen atom (free valence);

R_2 is chosen between the following groups:

- phenyl, optionally substituted with an halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;
- mono- or di-hydroxy substituted benzyl, preferably 3-4 di-hydroxy substituted benzyl;
- amidino group: $H_2N(C=NH)-$;
- the radical of formula (IIA), wherein optionally one unsaturation of ethylene type can be present between

the carbon atoms in position 1 and 2, or 3 and 4, or 4 and 5:



wherein:

p , p_1 , p_2 are integers, equal to or different from each other and are 0 or 1;

p_3 is an integer from 0 to 10;

R_4 is hydrogen, linear or branched C_1 - C_6 alkyl, free valence;

R_5 can have the following meanings:

- linear or branched C_1 - C_6 alkyl,
- C_3 - C_6 cycloalkyl,
- free valence,
- OR_A , wherein R_A has the following meanings:
 - linear or branched C_1 - C_6 alkyl optionally substituted with one or more halogen atoms, preferably F,
 - phenyl, optionally substituted with one halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;

R_6 , R_{6A} , R_7 , R_8 , equal or different, are H, methyl; or free valence;

with the proviso that in the radical of formula (IIA) when one unsaturation of ethylene type between C_1 and C_2 is present, R_4 and R_5 are free valences

such as to form the double bond between C_1 and C_2 ; when the unsaturation is between C_3 and C_4 , R_6 and R_7 are free valences such as to form the double bond between C_3 and C_4 ; when the unsaturation is between C_4 and C_5 , R_7 and R_8 are free valences such as to form the double bond between C_4 and C_5 ;

Q is equal to H , OH , OR_B wherein R_B is benzyl, a linear or branched C_1 - C_6 alkyl, optionally substituted with one or more halogen atoms, preferably F ; phenyl optionally substituted with one halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;

or Q can have one of the following meanings:

- C_3 - C_6 cycloalkyl;
- linear or branched C_1 - C_6 alkyl;
- guanidine ($H_2NC(=NH)NH-$);
- thioguanidine ($H_2NC(=S)NH-$);

in formula (II) R_2 with R_1 and with $W = C$ taken together form a C_4 - C_{10} , preferably C_6 , saturated or unsaturated, preferably saturated, ring.

When in formula (II) $W = C$, $m = 1$ and $R_0 = -(CH_2)_n-NH_2$ with $n = 1$, R_2 and R_1 with W as above defined form together the cyclohexane ring, in the radical A of formula (I) $T_1 = CO$ and the free valence of A is saturated with OH , the precursor drug of R is known as gabapentine;

when in formula (II) $W = C$, $m = 0$ and $R_0 = -(CH_2)_n-NH_2$ with $n = 0$, $R_1 = H$, R_2 is the radical of formula (IIA) wherein $p = p_1 = 1$, $p_2 = p_3 = 0$, $R_4 = R_5 = R_6 = R_{6A} = H$, $Q = H$, in the radical A of formula (I) $T_1 = CO$ and the free valence of A is saturated with OH , the precursor drug of R is known as norvaline;

when in formula (II) $W = C$, $m = 0$ and $R_0 = -(CH_2)_n-NH_2$ with $n = 0$, $R_1 = H$, R_2 is the radical of formula (IIA) wherein $p = p_1 = 1$, $p_2 = p_3 = 0$, $R_4 = R_5 = R_6 = R_{6A} = H$, Q is the guanidine group, in the radical A of formula (I) $T_1 = CO$ and the free valence of A is saturated with OH, the precursor drug of R is known as arginine;

when in formula (II) $W = C$, $m = 0$ and $R_0 = -(CH_2)_n-NH_2$ with $n = 0$, $R_1 = H$, R_2 is the radical of formula (IIA) wherein $p = p_1 = 1$, $p_2 = p_3 = 0$, $R_4 = R_5 = R_6 = R_{6A} = H$, Q is the thioguanidine group, in the radical A of formula (I) $T_1 = CO$ and the free valence of A is saturated with OH, the precursor drug of R is known as thiocitrulline;

when in formula (II) $W = C$, $m = 1$ and $R_0 = -(CH_2)_n-NH_2$ with $n = 1$, $R_1 = H$, R_2 is the radical of formula (IIA) wherein $p = p_1 = p_2 = p_3 = 0$, $R_4 = H$, $R_5 = Q = CH_3$, in the radical A of formula (I) $T_1 = CO$ and the free valence of A is saturated with OH, the precursor drug of R is known as pregabalin;

when in formula (II) $W = C$ and has configuration (S), $m = 1$ and $R_0 = -(CH_2)_n-NH_2$ with $n = 1$, $R_1 = H$, R_2 is the radical of formula (IIA) wherein $p = p_1 = p_2 = p_3 = 0$, $R_4 = H$, $R_5 = Q = CH_3$, in the radical A of formula (I) $T_1 = CO$ and the free valence of A is saturated with OH, the precursor drug of R is known as (S)-3-isobutylGABA;

when in formula (II) $W = C$, $m = 1$ and $R_0 = R_1 = H$, R_2 is the radical of formula (IIA) wherein $p = p_1 = 1$, $p_2 = p_3 = 0$, $R_4 = R_5 = R_6 = R_{6A} = H$, Q is the guanidine group, in the radical A of formula (I) $T_1 = NH$ and the free valence of A is saturated with H, the precursor drug of R is known as agmatine;

when in formula (II) $W = C$, $m = 2$ and $R_0 = -(CH_2)_n-NH_2$ with $n = 0$, $R_1 = H$, R_2 is the radical of formula (IIA) wherein $p = p_1$

$= p_2 = p_3 = 0$, R_4 and R_5 are free valences and between C_1 and C_2 there is one ethylene unsaturation, $Q = H$, in the radical A of formula (I) $T_1 = CO$ and the free valence of A is saturated with OH, the precursor drug of R is known as vigabatrin;

when in formula (II) $W = C$, $m = 0$ and $R_0 = -(CH_2)_n-NH_2$ with $n = 0$, $R_1 = H$, R_2 is the radical 3-4 di-hydroxy substituted benzyl, $T_1 = CO$ and the free valence of A is saturated with OH, the precursor drug of R is known as 2-amino-3-(3,4-dihydroxyphenyl)propanoic acid (dopa).

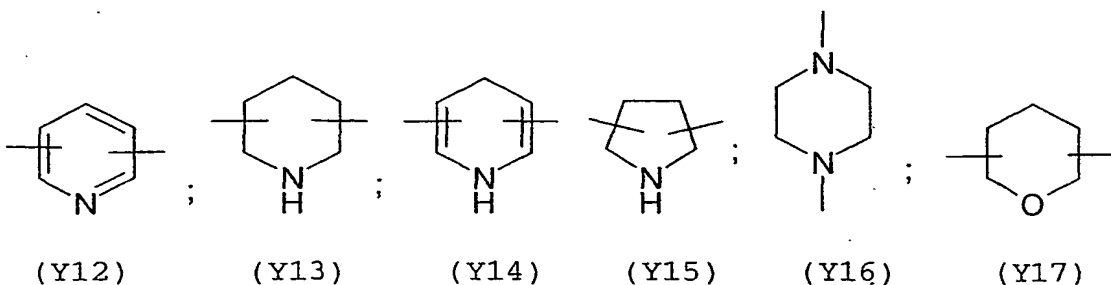
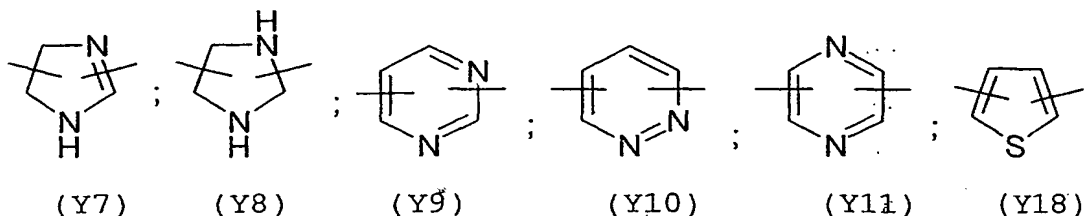
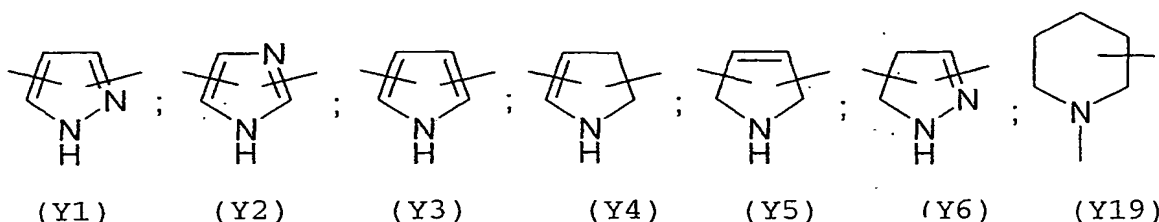
Other compounds used for the chronic pain which can be used as precursors of $A = R-T_1$ in formula (I) are lamotrigine, topiramate, tiagabine, zonisamide, carbamazepine, felbamate, amineptine, amoxapine, demexiptiline, desipramine, nortriptyline, opipramol, tianeptine.

Generally the precursor drugs of R are synthesized according to the methods reported in "The Merck Index, 12th Ed." (1996). When the precursor drugs of R comprise in the molecule the radical of formula (IIA), they can be synthesized as described in patent application WO 00/76958.

The precursor compounds of B of the above groups are prepared according to the methods known in the prior art and described, for example, in "The Merck Index, 12th Ed." herein incorporated by reference.

Preferably when in formula (I) $b_0 = 0$, Y in the bivalent linking group C is selected between Y_p and Y_{AR} as above defined.

Preferably Y^3 is selected from the following bivalent radicals:



The preferred of Y^3 are the following: (Y12), having the two free valences in the ortho position with respect to the nitrogen atom; (Y16) with the two valences linked to the two heteroatoms, Y1 (pyrazol) 3,5-disubstituted; (Y19), wherein the free valence on the ring is found in para position to the nitrogen atom.

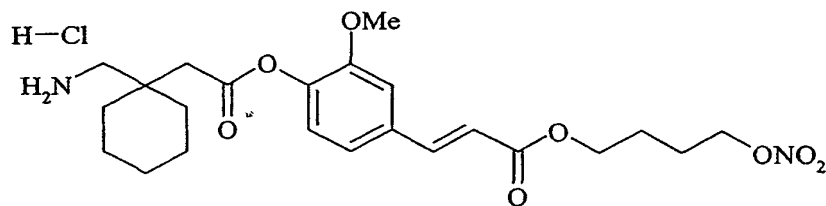
The precursors of Y as defined by formula (III), wherein the free valence of the oxygen is saturated with H and the free valence of the end carbon is saturated either with a carboxylic or hydroxyl group, are products available on the market or can be obtained by methods known in the prior art.

In formula (I) the preferred precursors of B for the synthesis of the nitrooxyderivatives usable in the present invention are the following: ferulic acid, N-acetylcysteine, cysteine, caffeic acid, hydrocaffeic and gentisic acid; the

preferred precursor drugs are the following: gabapentine, norvaline, arginine, pregabalin, (S)-3-isobutylGABA, agmatine.

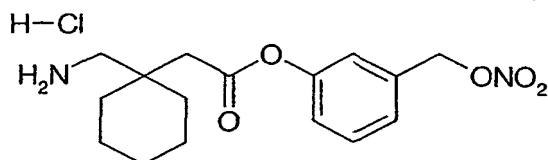
The preferred compounds of formula (I) according to the present invention are the following:

1-(aminomethyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XV)



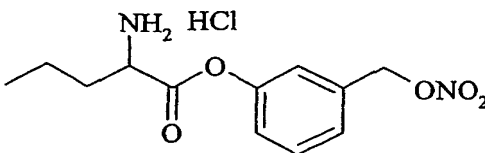
(XV)

1-(aminomethyl)cyclohexan acetic acid 3-(nitrooxymethyl) phenyl hydrochloride ester (XVI)



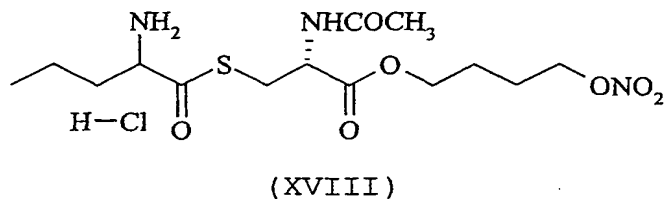
(XVI)

2-aminopentanoic acid 3-(nitrooxymethyl)phenyl hydrochloride ester (XVII)

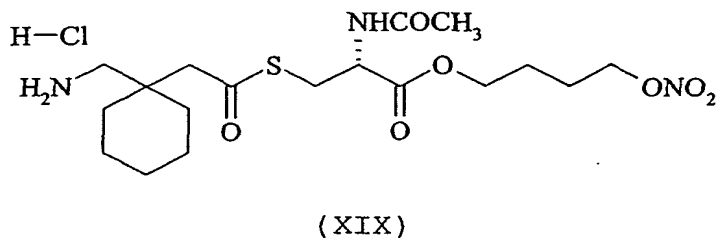


(XVII)

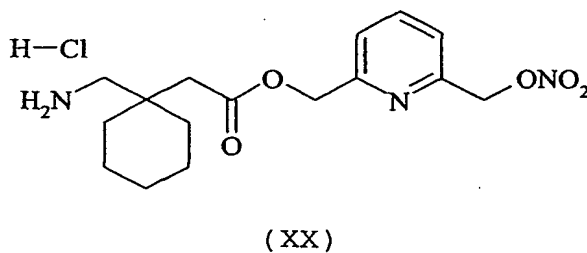
(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, 2-amino hydrochloride pentanoate (XVIII)



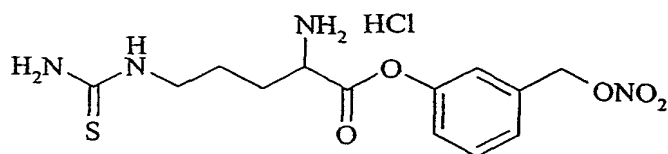
(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, 1-(aminomethyl)cyclohexanacetate hydrochloride (XIX)



1-(aminomethyl)cyclohexanacetic acid-, [6-(nitrooxy methyl)-2-pyridinyl]methyl hydrochloride ester (XX)

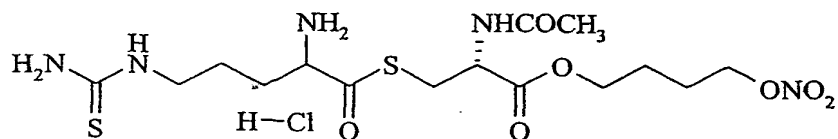


alpha-amino-delta-thioureidopentanoic acid, 3-(nitrooxy methyl)phenyl hydrochloride ester (XXI)



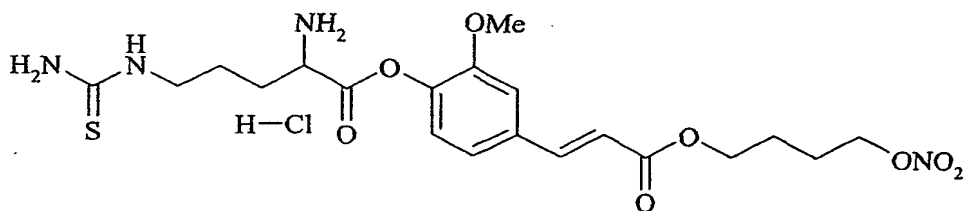
(XXI)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, alpha-amino-delta-thioureidopentanoate hydrochloride (XXII)



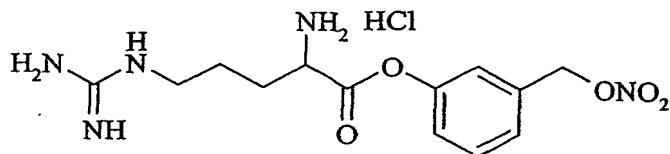
(XXII)

alpha-amino-delta-thioureidopentanoic acid, 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXIII)



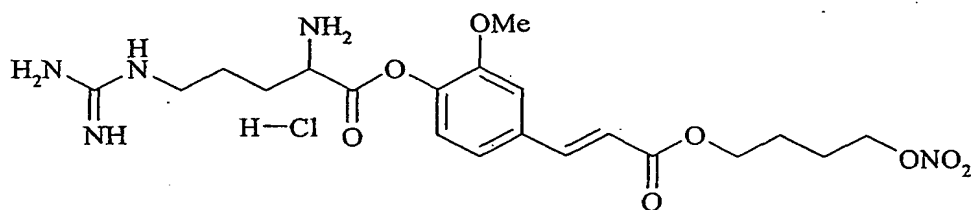
(XXIII)

2-amino-5-guanidinopentanoic acid, 3-(nitrooxy methyl)phenyl hydrochloride ester (XXIV)



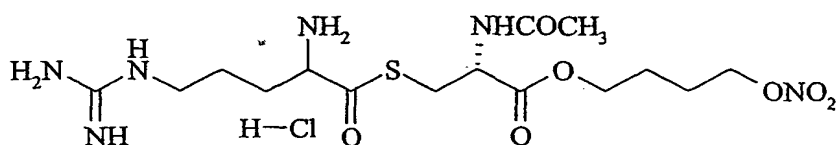
(XXIV)

2-amino-5-guanidinopentanoic acid-, 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXV)



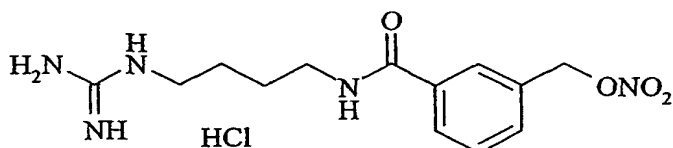
(XXV)

(S)-N-acetylcysteine-4-(nitrooxy)butyl ester, 2-amino-5-guanidinopentanoate hydrochloride (XXVI)



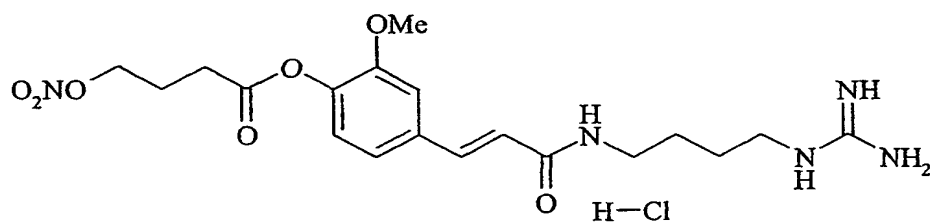
(XXVI)

4-(guanidine)butyl-3-nitrooxymethylbenzamide (XXVII)



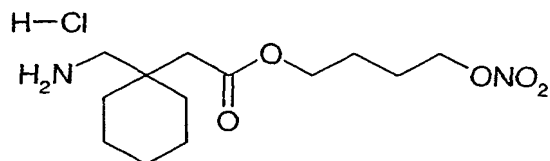
(XXVII)

4-(guanidine)butyl-3-[4-(4'-nitrooxybutyryloxy)-3-(methoxy)]phenyl-2-propenamide chloride (XXVIII)



(XXVIII)

1-(aminomethyl)cyclohexan acetic acid 4-(nitroxy)butyl
hydrochloride ester (XXIX)



(XXIX)

The preferred above compounds with formulas (XV) to (XXIX) can be used as nitrate salts.

The compounds according to the present invention, when they contain in the molecule one salifiable nitrogen atom, can be transformed into the corresponding salts by reaction in organic solvent such for example acetonitrile, tetrahydrofuran with an equimolar amount of the corresponding organic or inorganic acid.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acid.

Examples of inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acid.

Nitrate salts are preferred.

The compounds of the invention have shown to have an improved activity in the chronic pain treatment, in particular neuropathic, both at the central and peripheral nervous system level. Besides it has been surprisingly found by the Applicant that the invention compounds not only have an improved efficacy in reducing the neuropathic pain, but unexpectedly show also a lowering action of the progress of the pathological condition which causes the neuropathic pain. For example when the drugs of the present invention are administered to diabetic patients for reducing the diabetic neuropathic pain, it has been found that they are able not

only to reduce neuropathies, but also to reduce the complications caused by diabetes, for example affecting the blood vessels and/or the renal apparatus.

The compounds of the invention are particularly effective in the neuropathic pain treatment, for example the diabetic neuropathic pain, the post-infarct pain.

The compounds of the invention can also be used in combination or in admixture with NO-donor compounds of the prior art.

Said compounds contain for example in the molecule one or more ONO_2 or ONO groups.

The NO-donor compounds which can be used in combination with the invention compounds must comply with the test in vitro defined hereinafter.

The test relates to the nitric oxide generation from the NO-donors, for example nitroglycerin, niocorandil, nitroprussiate, etc., in the presence of endothelial cells (method a) or platelets (method b).

a) Endothelial cells

Human cells of the umbilical vein, cultured on plates, having a 10^3 density cells/well were incubated for 5 minutes with scalar concentrations of NO-donor (1-100 $\mu\text{g/ml}$). The incubation medium (physiologic solution, for example Tyrode) was then analyzed to determine the capability to generate NO of the compound under test, by means of:

- 1) nitric oxide detection by chemiluminescence;
- 2) cGMP determination (cyclic GMP n° 2715 of the above mentioned Merck).

For the analysis by chemiluminescence, an amount equal to 100 μ l was injected in the reaction chamber of a chemiluminescence analyzer containing glacial acetic acid and potassium iodide. The nitrites/nitrates present in the medium, under these conditions are converted into NO which is then detected after reaction with ozone, which produces light. In the equipments which measure the chemiluminescence, the luminescence produced is directly proportional to the generated NO levels and can be measured by a suitable photomultiplying unit of a chemiluminescence analyzer. The photomultiplier converts the incident light in electric voltage, which is quantitatively recorded. On the basis of a calibration curve, prepared with scalar nitrite concentrations, it can be quantitatively determined the generated NO amount. For example, from the incubation of 100 μ M of nicorandil, an amount equal to about 10 μ M of NO was generated.

For cGMP determination, an aliquot of the incubation medium (equal to 100 μ l) was centrifuged at 1,000 revolutions per 20 seconds. The supernatant was removed and the sediment treated with iced phosphate buffer (pH 7.4). The cGMP levels produced were tested by specific immuno-enzymatic reactants. From said experiments it resulted that, under these experimental conditions, the incubation with one of the various tested NO-donors caused a significant increase of cGMP with respect to the values obtained in absence of a NO-donor. For example, after an incubation with 100 μ M of sodium nitroprussiate, an increase of about 20 times the value obtained with the

incubation of the carrier alone without NO-donor was recorded.

b) Platelets

Washed human platelets, prepared substantially in the same way as described by Radomski et al, (Br. J. Pharmacol. 92, 639-1987), were used. 0.4 ml aliquots were incubated with NO-donor scalar concentrations (1-100 µg/ml) for 5 minutes. The incubation medium (for example Tyrode) was then analyzed to determine the capability of the tested compound to generate NO, by determination of nitric oxide by chemiluminescence and the cGMP determination, as described in the previous paragraph for the same analyses carried out on endothelial cells. For the determination by chemiluminescence, also in this case, on the basis of a calibration curve prepared with scalar nitrite concentrations, it was possible to quantitatively determine the produced NO amount. For example, after an incubation of 100 µM of nicorandil, an amount equal to 35 µM of NO was generated.

For cGMP determination, it resulted that also in these experimental conditions the incubation with one of the tested NO-donors gave a significant increase of cGMP with respect to the values obtained in absence of a NO-donor. For example, after an incubation with 100 µM of sodium nitroprussiate, an increase of about 30 times the value obtained with the incubation of the only carrier without NO-donor, was recorded.

The preferred NO-donor compounds are those containing in the molecule radicals of drugs belonging to the classes of aspirin, ibuprofen, paracetamol, naproxen, diclofenac,

flurbiprofen. The syntheses of these preferred compounds are described in patent applications WO 95/30641, WO 97/16405, WO 95/09831, WO 01/12584.

The compounds of the invention can be obtained by the methods described hereafter.

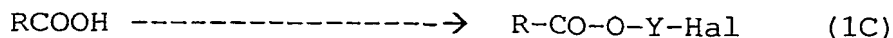
If in the drug molecule more reactive groups such for example COOH and/or HX are present, they must be usually protected before the reaction according to the methods known in the prior art; for example as described in the volume by Th. W. Greene: "Protective groups in organic synthesis", Harvard University Press, 1980.

The acylhalides are prepared according to the methods known in the prior art, for example by thionyl or oxalyl chloride, halides of P^{III} or P^V in solvents inert under the reaction conditions, such as for example toluene, chloroform, DMF, etc.

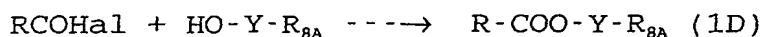
1) When in formula (I) $b_0 = 0$ and the free valence of the radical R of the drug is saturated with a carboxylic group, the synthesis methods to obtain the corresponding nitrooxyderivatives are the following:

1.A) The drug of formula RCOOH is treated with an agent activating the carboxyl group selected from N,N'-carbonyldiimidazol (CDI), N-hydroxybenzotriazol and dicyclohexylcarbodiimide (DCC) in solvent such as for example DMF, THF, chloroform, etc., at a temperature in the range from -5°C to 50°C and reacted in situ with a compound HO-Y-Hal, wherein Y and Hal are as above defined.

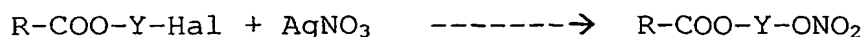
DCC, HO-Y-Hal



- 1.B) In alternative, the drug acylhalide is reacted with a compound HO-Y-R_{8A} , wherein Y is as above, R_{8A} is OH or a halogen in the presence of a base, in an organic solvent inert under the reaction conditions according to the scheme below reported:



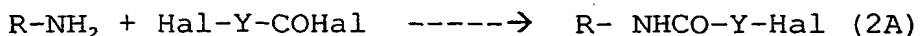
- 1.C) When the compounds obtained in the above reactions have formula R-COO-Y-Hal the corresponding nitrooxyderivatives are obtained by reacting the compound R-CO-O-Y-Hal with AgNO_3 in organic solvent such as acetonitrile, tetrahydrofuran according to the scheme:



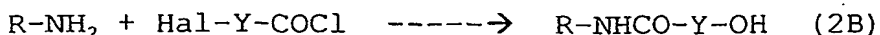
- 1.D) When the compounds obtained in the above reactions have formula R-COO-Y-OH the hydroxyl group is subjected to halogenation, for example with PBr_3 , PCl_5 , SOCl_2 , PPh_3 + I_2 , and then reacted with AgNO_3 in organic solvent such as acetonitrile, tetrahydrofuran.

- 2) When in formula (I) $b_0 = 0$, and the reactive function of the drug is the group NH_2 , the synthesis methods to obtain the corresponding nitrooxyderivatives are the following:

- 2.a) By reaction of the drug R-NH_2 with an acyl halide of formula Hal-Y-COHal , wherein Y and Hal are as above, according to the scheme:



- 2.b) By reaction of the drug R-NH_2 with an acyl halide of formula OH-Y-COHal , wherein Y and Hal are as above, according to the scheme:

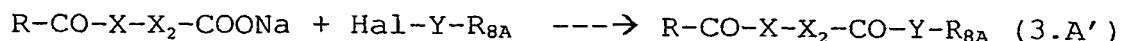


- 2.c) When the compounds obtained in the above reactions have formula R-NHCO-Y-Hal or R-NHCO-Y-OH the corresponding

nitrooxyderivatives are obtained as above described in 1.C and 1.D respectively.

3. When in formula (I) $b_0 = c_0 = 1$, and the free valence of the radical R of the drug is saturated with a carboxylic group, the synthesis methods to obtain the corresponding nitrooxyderivatives are the following:

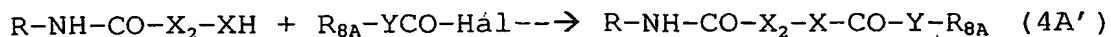
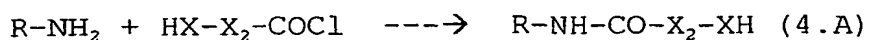
- 3.a) Alternatively, the acyl halide of the drug and the compound of formula $HX-X_2-COOH$, wherein X and X_2 are as above, are reacted according to the methods known in the prior art, to give the compound $R-CO-X-X_2-COOH$ which is transformed into the corresponding sodic salt and reacted with a compound of formula $Hal-Y-R_8$ wherein Hal and Y are as above and R_8 is Cl, Br, Iodine, OH:



When $R_{8A} = OH$ the compound of formula (3.A') is subjected to halogenation as above described in 1.D; when $R_{8A} = Hal$ the compound of formula (3.A') is reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran:

- 3.b) When Y_T is a C_4 linear alkylene, the precursor of B of formula $HO-X_2-COOH$ is reacted with triphenylphosphine in the presence of a halogenating agent such as CCl_4 or N-bromosuccinimide in tetrahydrofuran to give the compound of formula $HO-X_2-COO(CH_2)_4Br$ which is reacted with the molecule of the drug $RCOOH$ as described in 1.A and 1.C.
- 4) When in formula (I) $p = 1$ $b_0 = c_0 = 1$, and the reactive function of the drug is the group NH_2 , the synthesis methods to obtain the corresponding nitrooxyderivatives are the following:

- 4.a) Reaction of the drug $R-NH_2$ with an acyl halide of formula $HX-X_2-COHal$, wherein X and X_2 are as above, according to the methods known in the prior art, to give the compound $R-NH-CO-X_2-XH$ which is reacted with a compound of formula $R_{8A}-Y-COHal$ wherein R_{8A} and Y are as above.



- 4.b) Alternatively, the drug $R-NH_2$ is reacted with a compound of formula $HX-X_2-COOH$, wherein X and X_2 are as above, in the presence of dicyclohexylcarbodiimide as described in 1.A, to give the compound $R-NH-CO-X_2-XH$, which is reacted with a compound of formula $R_{8A}-Y-COCl$ wherein R_{8A} and Y are as above defined, to give the following compound: $R-NH-CO-X_2-X-CO-Y-R_{8A}$ (4.B)

When $R_{8A} = OH$ the compound of formula (4.B) or of formula (4a') is subjected to halogenation as above described in 1.D; when $R_{8A} = Hal$ the compound of formula (4.B) is reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran.

When the compounds of the present invention have one or more chiral centres, they can be used in a racemic form, as mixtures of diastereoisomers or enantiomers, as single enantiomers or single diastereoisomers. If the compound shows geometric asymmetry, the compound in the cis or trans form can be used.

The compounds object of the present invention are formulated in the corresponding pharmaceutical compositions for parenteral, oral and topical use according the techniques well known in the field, together with the usual excipients,

see for example the volume "Remington's Pharmaceutical Sciences 15th Ed."

The amount on a molar basis of the active principle in said formulations is the same or lower than the maximum posology indicated for the precursor drugs. Also higher doses can be used, considering their very good tolerability.

The daily administrable doses are those of the precursor drugs, or in case lower. The daily doses can be found in the publications of the field, such as for example in "Physician's Desk reference".

A further object of the invention is the use of analgesic drugs for the treatment of the chronic pain, in particular the neuropathic pain, in combination with NO-donor compounds as above defined.

The radicals of the conventional analgesic drugs for the chronic pain have been indicated above with R wherein the free valence is saturated with T_{1A} , wherein $T_{1A} = COZ_1$ wherein $Z_1 = SH, OZ, NHR_{1C}, XZ$, wherein Z, R_{1C} and X are as above defined.

Said compounds of formula $RCOZ_1$ are the precursor drugs of R.

It has been found that the combination of the precursor drugs of R in combination with the NO-donor compounds shows a synergic effect, whereby it is possible to use a lower amount of the analgesic compound for the chronic pain, whereby the side effects are reduced.

Besides the above mentioned precursor drugs of R, the following ones can be mentioned: lamotrigine, topiramate, tiagabine, zonisamide, carbamazepine, felbamate, amineptine, amoxapine, demexiptiline, desipramine, nortriptyline, opipramol, tianeptine, amitriptyline, butriptyline,

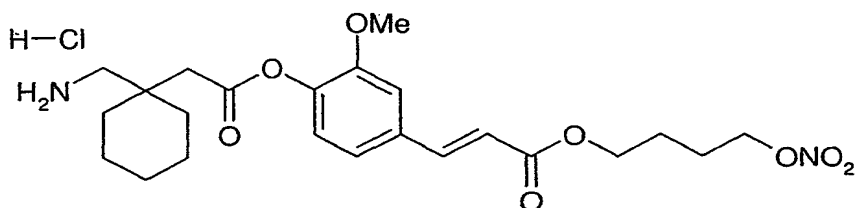
clomipramine, dibenzepin, dimetacrine, dothiepin, doxepin, fluacizine, imipramine, iprindole, lofepramine, melitracen, noxiptilin, propizepine, protriptyline, trimipramine.

The NO-donor compounds are as above defined.

The following Examples illustrate the invention without limiting the scope thereof.

EXAMPLE 1

Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XV)



A) Synthesis of the 1-(N-tert-butoxycarbonylaminomethyl)cyclohexan acetic acid

To a solution of 1-(aminomethyl)cyclohexanacetic acid (10 g, 58.4 mmol) in a mixture of dioxane (100 ml) and water (150 ml), triethylamine (16.27 ml, 116.8 mmol) and di-tert-butyl dicarbonate (15.3 g, 70 mmol) are added. The reaction mixture is left at room temperature, under stirring for 4 hours. After the solution has been cooled to 0°C it is brought to pH 2 with HCl 5%. The precipitate is filtered and dried under vacuum. 15 g of the expected product are obtained as a white solid having m.p. = 125°-127°C

B) Synthesis of 2-methoxy-4-[(1E)-3-[4-(bromo)butoxy]-3-oxy-1-propenyl]phenol

To a solution of ferulic acid (11.6 g, 59.7 mmol) in tetrahydrofuran (400 ml) tetrabromomethane (39.62 g, 119.47 mmol) and triphenylphosphine (31.34 g, 119.47 mmol) are added. The obtained mixture is kept under stirring at room temperature for 5 hours, filtered and evaporated at reduced pressure. The crude residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 8 g of the expected compound are obtained as a yellow solid having m.p. = 86°-89°C

C) Synthesis of 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenol

To a solution of 2-methoxy-4-[(1E)-3-[4-(bromo) butoxy]-3-oxy-1-propenyl]phenol (8 g, 24.3 mmol) in acetonitrile (500 ml) silver nitrate (12.25 g, 72.9 mmol) is added. The reaction mixture is heated at 40°C for 12 hours sheltered from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 75/25. 4 g of the expected product are obtained as a yellow solid having m.p. = 65°-68°C

D) Synthesis of the 1-(N-tert-butoxycarbonylaminomethyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl ester

To a solution of 1-(N-tert-butoxycarbonylaminomethyl)cyclohexan acetic acid (2.5 g, 9.2 mmol) in chloroform (200 ml) and N,N-dimethylformamide (3 ml), 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenol (3.15 g, 10.1 mmol), dicyclohexylcarbodiimide (5.7 g, 27.6 mmol) and N,N-dimethylaminopyridine (33 mg, 0.27 mmol) are added.

The reaction mixture is left at room temperature for 3 hours under stirring, filtered and evaporated at reduced pressure. The obtained residue is treated with ethyl acetate and washed with water. The organic phase is dried with sodium sulphate and evaporated at reduced pressure. The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 9/1. 5 g of the expected compound are obtained as an oil.

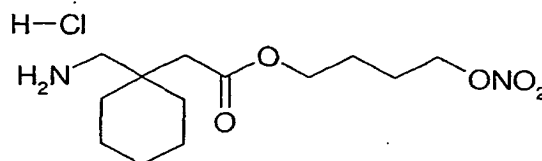
E) Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl ester (5 g, 8.8 mmoles) in ethyl acetate (100 ml) a solution HCl 1N in ethyl acetate (50 ml) is added. The reaction mixture is left overnight at room temperature, then concentrated under vacuum to a volume of 40 ml. The obtained residue is treated with ethyl ether. The precipitate is filtered and dried under vacuum. 1.8 g of the expected compound are obtained as a white solid having m.p. = 103°-105°C.

¹H-NMR (CDCl₃) ppm: 8.43 (2H, m); 7.55 (1H, d); 7.10 (3H, m); 6.34 (1H, d); 4.51 (2H, t), 4.26 (2H, t); 3.89 (3H, s); 3.12 (2H, s); 2.81 (2H, s); 1.82 (4H, m); 1.54 (10H, m).

EXAMPLE 2

Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 4-(nitrooxy)butyl hydrochloride ester



A) Synthesis of the 1-(N-tert-butoxycarbonylaminomethyl)cyclohexanecarboxylic acid 4-(bromo)butyl ester

To a solution of 1-(N-tert-butoxycarbonylaminomethyl)cyclohexanecarboxylic acid (1 g, 3.6 mmol) in N,N-dimethyl formamide (50 ml) cooled at 0°C, sodium ethylate (246 mg, 3.6 mmol) is added.

The reaction mixture is left at 0°C under stirring for 30 minutes and then 1,4-dibromobutane (1.28 ml, 10.8 mmol) is added. The solution is left under stirring overnight at room temperature, then diluted with ethyl ether and washed with water. The organic phase dried with sodium sulphate is evaporated under vacuum. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 0.7 g of the expected compound are obtained as an oil.

B) Synthesis of the 1-(N-tert-butoxycarbonylaminomethyl)cyclohexanecarboxylic acid 4-(nitrooxy)butyl ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl)cyclohexanecarboxylic acid 4-(bromo)butyl ester (1 g, 2.5 mmol) in acetonitrile (200 ml), silver nitrate (1.3 g, 7.5 mmol) is added. The reaction mixture is heated at 80°C for 6 hours sheltered from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 0.8 g of the expected compound are obtained as an oil.

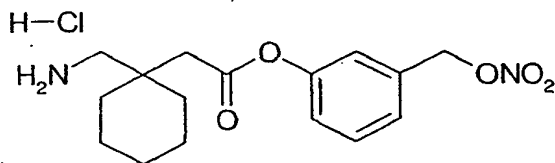
C) Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 4-(nitrooxy)butyl hydrochloride ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl)cyclohexan acetic acid 4-(nitrooxy)butyl ester (0.8 g, 2.06 mmol) in ethyl acetate (5 ml), a HCl 1N solution in ethyl acetate (20ml) is added. The reaction mixture is left for 3 hours at room temperature then is treated with n-hexane. The precipitate is filtered and dried under vacuum. 0.45 g of the expected compound are obtained as a white solid having m.p. = 80.3°-81.3°C

¹H-NMR (DMSO) ppm: 8.23 (2H, s); 4.58 (2H, t), 4.09 (2H, t); 2.92 (2H, s); 2.56 (2H, s); 1.74 (4H, m); 1.44 (10H, m).

EXAMPLE 3

Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 3-(nitrooxymethyl)phenyl hydrochloride ester (XVI)



A) Synthesis of 3-(bromomethyl)phenol

To a solution of 3-hydroxybenzyl alcohol (4 g, 32.2 mmol) in methylene chloride (250 ml), cooled at 0°C, tetrabromomethane (12.82 g, 38.6 mmol) and triphenylphosphine (12.67 g, 48.3 mmol) are added. The mixture is kept under stirring at 0°C for 10 minutes, then evaporated at reduced pressure. The crude product is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 3.5 g of the expected compound are obtained.

B) Synthesis of the 1-(N-tert-butoxycarbonylamino methyl)cyclohexan acetic acid 3-(bromomethyl) phenyl ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl)cyclohexan acetic acid (2.6 g, 9.7 mmols) in chloroform (200 ml) and N,N-dimethylformamide (2 ml), 4-(bromomethyl)phenol (2 g, 10.7 mmoli), dicyclohexylcarbodiimide (4 g, 19.7 mmols) and N,N-dimethylaminopyridine (24 mg, 0.20 mmols) are added. The reaction mixture is left at room temperature for 4 hours under stirring, filtered and evaporated at reduced pressure. The obtained residue is treated with ethyl acetate and washed with water. The organic phase is dried with sodium sulphate and evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 9/1. 1.4 g of the compound are obtained as an oil.

C) Synthesis of the 1-(N-tert-butoxycarbonylamino methyl)cyclohexan acetic acid 3-(nitrooxymethyl)phenyl ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl)cyclohexan acetic acid 3-(bromomethyl) phenyl ester (1.4 g, 3.18 mmols) in acetonitrile (300 ml) silver nitrate (1 g, 6.36 mmols) is added. The reaction mixture is heated at 50°C for 4 hours sheltered from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 0.75 g of the expected compound are obtained as an oil.

D) Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 3-(nitrooxymethyl)phenyl hydrochloride ester

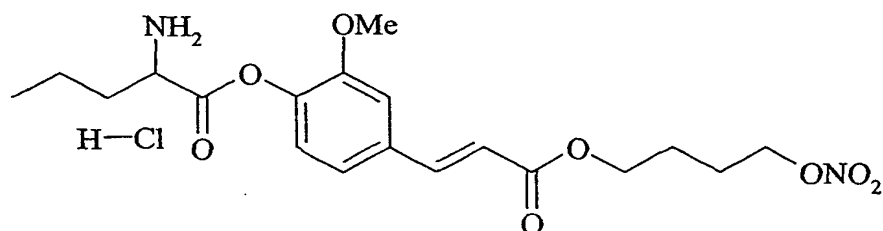
To a solution of 1-(N-tert-butoxycarbonylamino methyl)cyclohexan acetic acid 3-(nitrooxymethyl)phenyl ester

(0.75 g, 1.8 mmol) in ethyl acetate (5 ml), a HCl 1N solution in ethyl acetate (18 ml) is added. The reaction mixture is left for 15 minutes at room temperature, then it is treated with n-hexane. The precipitate is filtered and dried under vacuum. 0.45 g of the expected compound are obtained as a white solid having m.p. = 106°-108°C.

¹H-NMR (DMSO) ppm: 8.16 (3H, m); 7.52 (1H, t); 7.44 (1H, d); 7.34 (1H, s), 7.28 (1H, d); 5.65 (2H, s), 3.03 (2H, m); 2.86 (2H, s); 1.55 (10H, m).

EXAMPLE 4

Synthesis of the 2-aminopentanoic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester



A) Synthesis of the 1-(N-tert-butoxycarbonylamino) pentanoic acid

To a solution of 2-aminopentanoic acid (4 g, 34.14 mmol) in dioxane (40 ml) and water (75 ml), triethylamine (9.5 ml, 68.29 mmol) and di-tert-butyl dicarbonate (8.94 g, 49.97 mmol) are added. The reaction mixture is left at room temperature, under stirring for 17 hours. After having cooled the solution at 0°C, it is brought to pH = 2 with HCl at 5%. It is extracted with ethyl acetate, the joined organic phases are washed with water and dried with sodium sulphate.

The solvent is evaporated at reduced pressure to give the compound as an yellow oil which is used without further purification.

B) Synthesis of 2-methoxy-4-[(1E)-3-[4-(bromo)butoxy]-3-oxy-1-propenyl]phenol

To a solution of ferulic acid (11.6 g, 59.7 mmols) in tetrahydrofuran (400 ml), tetrabromomethane (39.62 g, 119.47 mmols) and triphenylphosphine (31.34 g, 119.47 mmols) are added. The obtained mixture is kept under stirring at room temperature for 5 hours, filtered and evaporated at reduced pressure. The obtained crude compound is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 8 g of the expected compound are obtained as a yellow solid having m.p. = 86°-89°C.

C) Synthesis of 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenol

To a solution of 2-methoxy-4-[(1E)-3-[4-(bromo) butoxy]-3-oxy-1-propenyl]phenol (8 g, 24.3 mmols) in acetonitrile (500 ml) silver nitrate (12.25 g, 72.9 mmols) is added. The reaction mixture is heated at 40°C for 12 hours sheltered from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 75/25. 4 g of the expected compound are obtained as a yellow solid having m.p. = 65°-68°C.

C) Synthesis of the 2-(N-tert-butoxycarbonylamino) pentanoic acid
2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl ester

To a solution of 2-(N-tert-butoxycarbonylamino) pentanoic acid (0.5 g, 2.3 mmol) in chloroform (12 ml), 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenol (0.86 g, 2.76 mmol), dicyclohexylcarbodiimide (0.52 g, 2.53 mmol) and N,N-dimethylaminopyridine (0.03 g, 0.23 mmol) are added. The reaction mixture is left at room temperature for 1 hour under stirring, filtered and evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 75/25. 0.5 g of the expected compound are obtained as an oil. Yield 43%.

D) Synthesis of the 2-aminopentanoic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester

To a solution of 2-(N-tert-butoxycarbonylamino) pentanoic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl ester (0.28 g, 0.548 mmol) in ethyl acetate (7 ml), a HCl solution in ethyl acetate (6.8 N, 0.700 ml) is added. The reaction mixture is left 3 hours at room temperature. The precipitate is filtered and dried under vacuum. 0.1 g of the expected compound are obtained as a white solid.

¹H-NMR (DMSO) ppm: 8.75 (3H, m); 7.62 (1H, d); 7.58 (1H, s); 7.3 (1H, d); 7.2 (1H, d); 6.72 (1H, d); 4.57 (2H, t), 4.26 (1H, t); 4.18 (2H, t); 3.82 (3H, s); 1.95 (2H, m); 1.75 (4H, m); 1.45 (2H, m); 0.98 (3H, m).

EXAMPLE F1

Evaluation of the analgesic activity of the invention compounds by the "paw-licking" test

Four groups of Swiss male mice (20-25 g, Charles River) each formed by 10 animals, received by intraperitoneal

injection Gabapentin (90 mg/kg) or the compound of formula (XVI) (Example 3), called NO-Gabapentin at the doses of 50 mg/kg, in a saline solution. The control group received the same volume of saline solution. One hour after the administration of the compound solutions, formalin (10 μ l) was injected in the paw. In the 15 minutes subsequent to formalin administration, for each animal, the number of times wherein it licked its paw was counted. The analysis was carried out "in blind".

The results reported in Table 1 are expressed as percentage ratio between the number of times wherein the "paw-licking" was observed in the treated animals to that of the control group.

The results show that the NO-gabapentin is more active than the starting drug in inhibiting the "paw-licking".

EXAMPLE F2

Evaluation of the analgesic activity of the drugs used in the chronic (neuropathic) pain treatment combined with a nitric oxide-donor drug.

Wistar adult rats weighing about 200 grams were used, in the experimental model described by Bennett GJ, Xie YK, Pain 1988, 33(1): 87-107. The pain response (withdrawal latencies) is determined 14 days after the ligature of the right sciatic nerve. The results obtained are reported in Table 2 and have been expressed as a percentage ratio of the difference between the response from the intact paw and from the injured paw, to the response of the control animals, that have been injected with the carrier and undergone the nerve ligature. The groups were of 10 rats each. The animals in each of the treated groups received, respectively, the following drugs at the

indicated doses:

- clomipramine 10 mg/kg i.p.,
- 2-acetylsalicylic acid (3-nitrooxymethyl)phenyl ester (ASA-NO) 100 mg/Kg p.o.
- clomipramine + NO-ASA at the above indicated doses.

NO-ASA was prepared as described in patent application WO 97/16405.

The results are reported in Table 2 and show that the mixture of the analgesic drug with the nitrooxyderivative synergically increases the analgesic effect.

EXAMPLE F3

Acute toxicity of gabapentin and NO-gabapentin in the diabetic animal

In 50 Wistar adult male rats weighing 165-190 g, diabetes was induced by injection i.v. of a single dose of streptozocin (65 mg/kg in 1 ml/kg buffer citrate at pH 4.5).

After one week the animals were distributed in three groups of 10 rats each and treated per os for three days with daily doses of 100 mg/kg of gabapentin and NO-gabapentin. The controls were treated only with streptozocin.

Death rate was monitored for 7 days from the last treatment.

The results are indicated in Table 3.

The Table shows that death rate in the diabetic animals administered with NO-gabapentin is less than half with respect to the animals treated with gabapentin.

EXAMPLE F 4

In this experiment the effect of acute administration of NO-gabapentin was assessed and compared with that of the

precursor drug, gabapentin, in a rat model of neuropathic pain.

In 6 groups of female Sprague-Dawley rats weighting 200 g, photochemically-induced ischemic spinal cord injury was produced according to methods described by Xu et al. Pain, 1992, 48, 279-290. Spinally-injured rats developed a chronic pain syndrome, including marked mechanical and cold allodynia. The rats were injured 3-6 months before the beginning of the experiment.

Each group of rats was i.p. treated, respectively, with one of the following compounds using one of the above indicated doses:

- NO-gabapentin at doses of 20 mg/Kg (55 μ mole/Kg), or 60 mg/Kg (167,21 μ mole/Kg), or 100 mg/kg (278,7 μ mole/Kg), dissolved in saline, single dose, i. p.);
- gabapentin at doses of 30 mg/Kg (175 μ mole/Kg) or 100 mg/kg (584 μ mole/Kg), dissolved in saline, single dose i. p.);
- the control group received the vehicle;

The response to cold was tested by spray-applying ethyl chloride on the shaved allodynic skin area at time 0(i.p. injection) and then at 30', 120' and 240'. The response was evaluated according to the following score:

- 0 = no response;
- 1 = localized response (skin twitch and contraction), no vocalization;
- 2 = transient vocalization, moderate struggle;
- 3 = sustained vocalization and aggression.

The results are reported in Table 4 and show that acute administration of NO-gabapentin alleviated in a dose-dependent way cold allodynia.

The effect of the compounds on motor activity was also evaluated using a combined testing system as described in Hao, J.X. and Xu, X. J., Pain, 1996, 66, 279-286.

Table 5 reports the results on motor performance of the same groups of rats i.p. injected.

When the score found in the treated group is comparable to that of the control groups it means that the animals of the treated group are not impaired as to motor activity and are not sedated.

Comments on Tables 4 and 5

Table 4 shows that the effect of NO-gabapentin was significant and lasted 120 min with the dose of 60 mg/kg (167,21 μ mole/Kg) and 240 min with the dose of 100 mg/kg (278,7 μ mole/Kg). The vehicle produced no effect. Gabapentin at the dose of 30 mg/Kg (175 μ mole/Kg) did not produce a significant antiallodynic effect (Table 4). At the dose of 100 mg/kg (584 μ mole/Kg), induced motor impairment and sedation (Table 5), which made it difficult to evaluate its anti-allodynic effect.

EXAMPLE F 5

In this experiment the effect of repeated administration of NO-gabapentin was assessed and compared with that of the precursor drug gabapentin in a rat model of neuropathic pain. In 4 groups of female Sprague-Dawley rats weighting 200 g photochemically-induced ischemic spinal cord injury was produced according to methods describe by Xu et al. Pain, 1992, 48, 279-290.

Spinally-injured rats developed a chronic pain syndrome, including marked mechanical and cold allodynia. The rats were injured 3-6 months before the beginning of the experiment. Each of the groups of rats were i.p. treated daily for 10 day, respectively, with 60 mg/kg (167,2 μ mole/Kg) of NO-gabapentin and with 30 mg/Kg (175 μ mole/Kg) of gabapentin. Controls (two groups) received only the vehicle. Each day the treatment of the animals was made at the same time. During the experiment vocalized thresholds to graded mechanical touch/pressure were tested with von Frey hairs.

During testing, rats were gently restrained in a standing position and the von Frey hair was pushed onto the skin until filament becomes bent. The frequency of stimulation was about 1/s and repeated 5-10 times. The intensity of stimulation (g) which induced consistent vocalization (> 75% response rate) is considered as pain threshold. Behavioral testings were carried out before the daily for the control group and 1 hour after administration for the treated groups.

The effect of chronic daily administration of gabapentin and NO-gabapentin is reported in Table 6.

NO- gabapentin alleviated mechanical allodynia following the first administration and a significant effect was maintained up to day 6. Gabapentin did not produce a significant effect up to the second day and the effect was lower than that of NO-gabapentin.

Table 1

Evaluation of the analgesic activity of gabapentin and of the NO-gabapentin derivative in the experiment F1 (rats injected in a paw with formalin)		
Treatment	Dose (mg/kg)	Number "paw licking" %
Controls		100
Gabapentin	90	80
NO-Gabapentin	50	70

Table 2

Ex. F2 :analgesic activity of the drugs used in the chronic (neuropathic) pain treatment in combination with a nitric oxide-donor drug	
Treatment	response %
Controls	100
Clomipramine	72
NO-ASA	82
Clomipramine + NO-ASA	29

Table 3

Rex. F3 : acute toxicity of gabapentin and NO-gabapentin in diabetic rats	
Treatment	lethality %
Controls	10
Gabapentin	50
NO-gabapentin	20

Table 4

Ex. F4 : effect of different doses of NO-gabapentin and gabapentin on cold stimulation in a rat model of neuropathic pain. Response is evaluated with by a score (0-3).					
Compound	Dose (μ mole/kg)	Time (min)			
		0	30	120	240
Control	-	2	2	2	2
NO-gabapentin	55.7	2	2	2	-
NO-gabapentin	167.2	2	1	1	-
NO-gabapentin	278.7	2	1	1	1
Gabapentin	175	2	2	2	2
gabapentin	584	-	-	-	-

Table 5

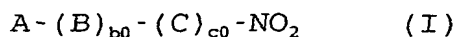
Ex. F4 :effect of different acute doses of NO-gabapentin and gabapentin on motor performance in a rat model of neuropathic pain.					
Compound	Dose (μ mole/ kg)	Time (min)			
		0	30	120	240
Control	-	15	15	15	15
NO-gabapentin	55.7	14	14	14	-
NO-gabapentin	167.2	14	14	15	-
NO-gabapentin	278.7	14	15	14	14
Gabapentin	175	20	20	20	20
Gabapentin	584	15	30	30	25

Table 6

Ex. F5 :effect of repeated administration of NO-gabapentin and gabapentin on vocalization threshold (g) to mechanical stimulation with von Frey hairs in a rat model of neuropathic pain.					
Compound	Dose (μ mole/kg)	Day			
		1	2	4	6
Baseline	-	2	5	8	2
NO-gabapentin	167.2	100	200	400	90
Baseline	-	5	3	3	5
Gabapentin	175	5	6	70	90

CLAIMS

1. Nitrooxyderivative compounds or salts thereof having the following general formula (I):



wherein:

c_0 is an integer and is 0 or 1, preferably 1;

b_0 is an integer and is 0 or 1, with the proviso that c_0 and b_0 cannot be contemporaneously equal to zero;

$A = R-T_1-$, wherein R is the radical of an analgesic drug for the chronic pain, in particular for the neuropathic pain;

$T_1 = (CO)_t$ or $(X)_{t'}$, wherein $X = O, S, NR_{1c}$, R_{1c} is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, t and t' are integers and equal to zero or 1, with the proviso that $t = 1$ when $t' = 0$; $t = 0$ when $t' = 1$;

$B = -T_B-X_2-T_{BI}-$ wherein

T_B and T_{BI} are equal or different;

$T_B = (CO)$ when $t = 0$, $T_B = X$ when $t' = 0$, X being as above;

$T_{BI} = (CO)_{tx}$ or $(X)_{txx}$, wherein tx and txx have the value of 0 or 1; with the proviso that $tx = 1$ when $txx = 0$; and $tx = 0$ when $txx = 1$; X is as above;

X_2 , bivalent radical, is such that the corresponding precursor of $B -T_B-X_2-T_{BI}-$ wherein the free valences of T_B and of T_{BI} are saturated each with OZ , with Z or with $-N(Z^I)(Z^{II})$, being:

$Z = H, C_1-C_{10}$, preferably C_1-C_5 alkyl linear or branched when possible,

Z^I , Z^{II} equal to or different have the values of Z as above, depending on that T_b and/or $T_{bt} = CO$ or X , in function of the values of t , t' , tx and txx ;

the precursor compound of B as above defined being selected from the following classes of compounds:

- aminoacids, selected from the following: L-carnosine, anserine, selenocysteine, selenomethionine, penicillamine, N-acetylpenicillamine, cysteine, N-acetylcysteine, glutathione or esters thereof, preferably ethyl or isopropyl ester;
- hydroxyacids, selected from the following: gallic acid, ferulic acid, gentisic acid, citric acid, caffeic, dihydrocaffeic acid, p-cumaric acid, vanillic acid;
- aromatic and heterocyclic polyalcohols, selected from the following: nordihydroguaiaretic acid, quercetin, catechin, kaempferol, sulfurethyne, ascorbic acid, isoascorbic acid, hydroquinone, gossypol, reductic acid, methoxyhydroquinone, hydroxyhydroquinone, propyl gallate, saccharose, 3,5-di-tertbutyl-4-hydroxybenzylthio glycolate, p-cumaric alcohol, 4-hydroxy-phenylethyl alcohol, coniferyl alcohol, allopurinol;
- compounds containing at least one free acid function, selected from the following: 3,3'-thiodipropionic acid, fumaric acid, dihydroxymaleic acid, edetic acid;

$C =$ bivalent radical $-T_c-Y-$ wherein

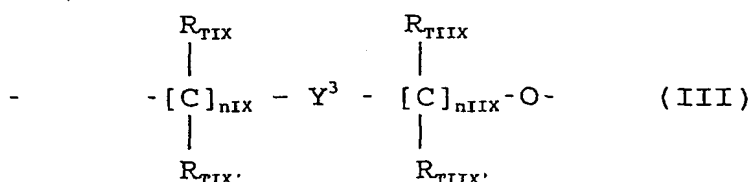
when $b_0 = c_0 = 1$: $T_c = (CO)$ when $tx = 0$, $T_c = X$ when $txx = 0$, X being as above defined,

when $b_0 = 0$: $T_c = (CO)$ when $t = 0$, $T_c = X$ when $t' = 0$, X being as above defined,

when $c_0 = 0$: $tx = 0$, $T_{BI} = X = -O-$;

Y has one of the following meanings:

Y_p :



wherein:

nIX is an integer from 0 to 5, preferably 1;

$nIIX$ is an integer from 1 to 5 preferably 1;

R_{TIX} , $R_{TIX'}$, R_{TIIX} , $R_{TIIX'}$, equal to or different from each other are H or linear or branched C_1 - C_4 alkyl; preferably R_{TIX} , $R_{TIX'}$, R_{TIIX} , $R_{TIIX'}$ are H;

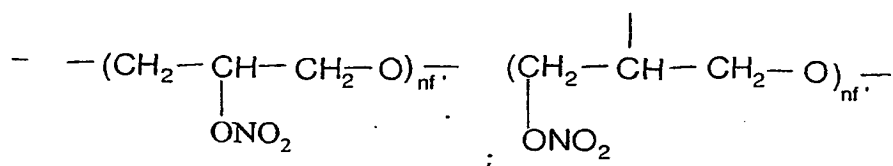
Y^3 is a saturated, unsaturated or aromatic heterocyclic ring, having 5 or 6 atoms, containing from one to three heteroatoms, preferably from one to two, said heteroatoms being equal or different and selected from nitrogen, oxygen, sulphur;

or Y can be:

Y_0 , selected from the following:

an alkyleneoxy group $R'O$ wherein R' is a linear or branched when possible C_1 - C_{20} , having preferably from 2 to 6 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be substituted by heteroatoms, the ring can have side chains of R' type, R' being as above;

or Y is selected from one of the following groups:



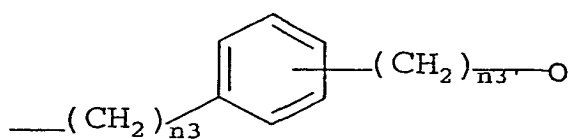
wherein nf' is an integer from 1 to 6 preferably from 1 to 4;



wherein $\text{R}_{1f} = \text{H}, \text{CH}_3$ and nf is an integer from 1 to 6; preferably from 2 to 4;

Y_{AR} , selected from:

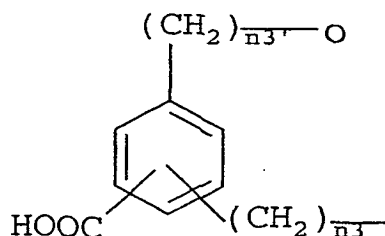
Y_{AR1} :



(V)

wherein n3 is an integer from 0 to 5 and $\text{n3}'$ is an integer from 1 to 3; or

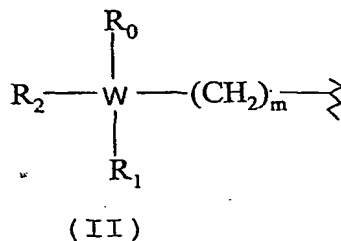
Y_{AR2} :



(VI)

wherein n3 and $\text{n3}'$ have the above meaning.

2. Compounds according to claim 1, wherein the radical R is that of chronic analgesic drugs, in particular of drugs for the neuropathic pain.
3. Compounds according to claims 1-2, wherein R is the radical of an analgesic drug, having formula II:



wherein:

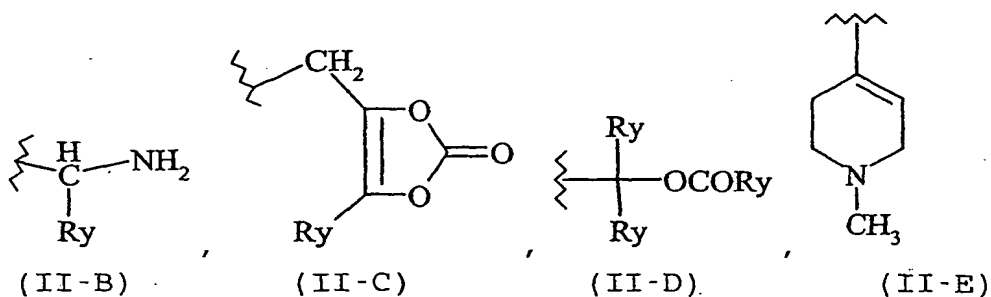
W is a carbon atom or a nitrogen atom;

m is an integer from 0 to 2;

$R_0 = H, -(CH_2)_n-NHR_{1A}$, n being an integer from 0 to 2, wherein

$R_{1A} = H, -C(O)-R_{1H}, -C(O)O-R_{1H}$, wherein

R_{1H} is a linear or branched C_1 - C_{10} alkyl, a phenyl or benzyl group; or R_{1H} has one of the following meanings:

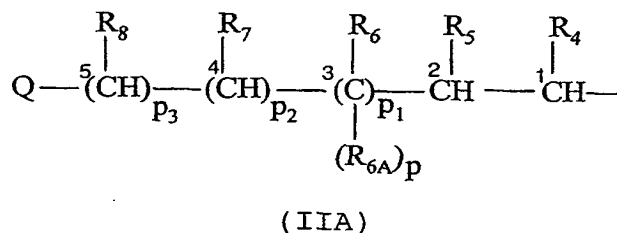


wherein Ry is hydrogen, a linear or branched C_1 - C_{10} alkyl, a phenyl or benzyl group;

$R_1 = H$, when $W = N$, R_1 is the electronic doublet on the nitrogen atom (free valence);

R₂ is chosen between the following groups:

- phenyl, optionally substituted with an halogen atom or with one of the following groups: -OCH₃, -CF₃, nitro;
- mono- or di-hydroxy substituted benzyl, preferably 3-4 di-hydroxy substituted benzyl;
- amidino group: H₂N(C=NH)-;
- the radical of formula (IIA), wherein optionally one unsaturation of ethylene type can be present between the carbon atoms in position 1 and 2, or 3 and 4, or 4 and 5:



wherein:

P, P₁, P₂ are integers, equal to or different from each other and are 0 or 1;

P₃ is an integer from 0 to 10;

R₄ is hydrogen, linear or branched C₁-C₆ alkyl, free valence;

R₅ can have the following meanings:

- linear or branched C₁-C₆ alkyl,
- C₃-C₆ cycloalkyl,
- free valence,
- OR_A, wherein R_A has the following meanings:

- linear or branched C₁-C₆ alkyl optionally substituted with one or more halogen atoms, preferably F,
- phenyl, optionally substituted with one halogen atom or with one of the following groups: -OCH₃, -CF₃, nitro;

R₆, R_{6A}, R₇, R₈, equal or different, are H, methyl; or free valence;

with the proviso that in the radical of formula (IIA) when one unsaturation of ethylene type between C₁ and C₂ is present, R₄ and R₅ are free valences such as to form the double bond between C₁ and C₂; when the unsaturation is between C₃ and C₄, R₆ and R₇ are free valences such as to form the double bond between C₃ and C₄; when the unsaturation is between C₄ and C₅, R₇ and R₈ are free valences such as to form the double bond between C₄ and C₅;

Q is equal to H, OH, OR_B wherein R_B is benzyl, a linear or branched C₁-C₆ alkyl, optionally substituted with one or more halogen atoms, preferably F, phenyl optionally substituted with one halogen atom or with one of the following groups: -OCH₃, -CF₃, nitro;

or Q can have one of the following meanings:

- C₃-C₆ cycloalkyl;
- linear or branched C₁-C₆ alkyl;
- guanidine (H₂NC(=NH)NH-);
- thioguanidine (H₂NC(=S)NH-);

in formula (II) R_2 with R_1 and with $W = C$ taken together form a C_4 - C_{10} , preferably C_6 , saturated or unsaturated, preferably saturated, ring.

4. Compounds according to claim 3, wherein:

when in formula (II) $W = C$, $m = 1$ and $R_0 = -(\text{CH}_2)_n\text{-NH}_2$ with $n = 1$, R_2 and R_1 with W as above defined form together the cyclohexane ring, in the radical A of formula (I) $T_1 = \text{CO}$ and the free valence of A is saturated with OH, the precursor drug of R is known as gabapentine;

when in formula (II) $W = C$, $m = 0$ and $R_0 = -(\text{CH}_2)_n\text{-NH}_2$ with $n = 0$, $R_1 = H$, R_2 is the radical of formula (IIA) wherein $p = p_1 = 1$, $p_2 = p_3 = 0$, $R_4 = R_5 = R_6 = R_{6A} = H$, $Q = H$, in the radical A of formula (I) $T_1 = \text{CO}$ and the free valence of A is saturated with OH, the precursor drug of R is known as norvaline;

when in formula (II) $W = C$, $m = 0$ and $R_0 = -(\text{CH}_2)_n\text{-NH}_2$ with $n = 0$, $R_1 = H$, R_2 is the radical of formula (IIA) wherein $p = p_1 = 1$, $p_2 = p_3 = 0$, $R_4 = R_5 = R_6 = R_{6A} = H$, Q is the guanidine group, in the radical A of formula (I) $T_1 = \text{CO}$ and the free valence of A is saturated with OH, the precursor drug of R is known as arginine;

when in formula (II) $W = C$, $m = 0$ and $R_0 = -(\text{CH}_2)_n\text{-NH}_2$ with $n = 0$, $R_1 = H$, R_2 is the radical of formula (IIA) wherein $p = p_1 = 1$, $p_2 = p_3 = 0$, $R_4 = R_5 = R_6 = R_{6A} = H$, Q is the thioguanidine group, in the radical A of formula (I) $T_1 = \text{CO}$ and the free valence of A is saturated with OH, the precursor drug of R is known as thiocitrulline;

when in formula (II) $W = C$, $m = 1$ and $R_0 = -(\text{CH}_2)_n\text{-NH}_2$ with $n = 1$, $R_1 = H$, R_2 is the radical of formula (IIA) wherein $p = p_1 = p_2 = p_3 = 0$, $R_4 = H$, $R_5 = Q = \text{CH}_3$, in the

radical A of formula (I) $T_1 = \text{CO}$ and the free valence of A is saturated with OH, the precursor drug of R is known as pregabalin;

when in formula (II) $W = \text{C}$ and has configuration (S), $m = 1$ and $R_0 = -(\text{CH}_2)_n\text{-NH}_2$ with $n = 1$, $R_1 = \text{H}$, R_2 is the radical of formula (IIA) wherein $p = p_1 = p_2 = p_3 = 0$, $R_4 = \text{H}$, $R_5 = Q = \text{CH}_3$, in the radical A of formula (I) $T_1 = \text{CO}$ and the free valence of A is saturated with OH, the precursor drug of R is known as (S)-3-isobutylGABA;

when in formula (II) $W = \text{C}$, $m = 1$ and $R_0 = R_1 = \text{H}$, R_2 is the radical of formula (IIA) wherein $p = p_1 = 1$, $p_2 = p_3 = 0$, $R_4 = R_5 = R_6 = R_{6A} = \text{H}$, Q is the guanidine group, in the radical A of formula (I) $T_1 = \text{NH}$ and the free valence of A is saturated with H, the precursor drug of R is known as agmatine;

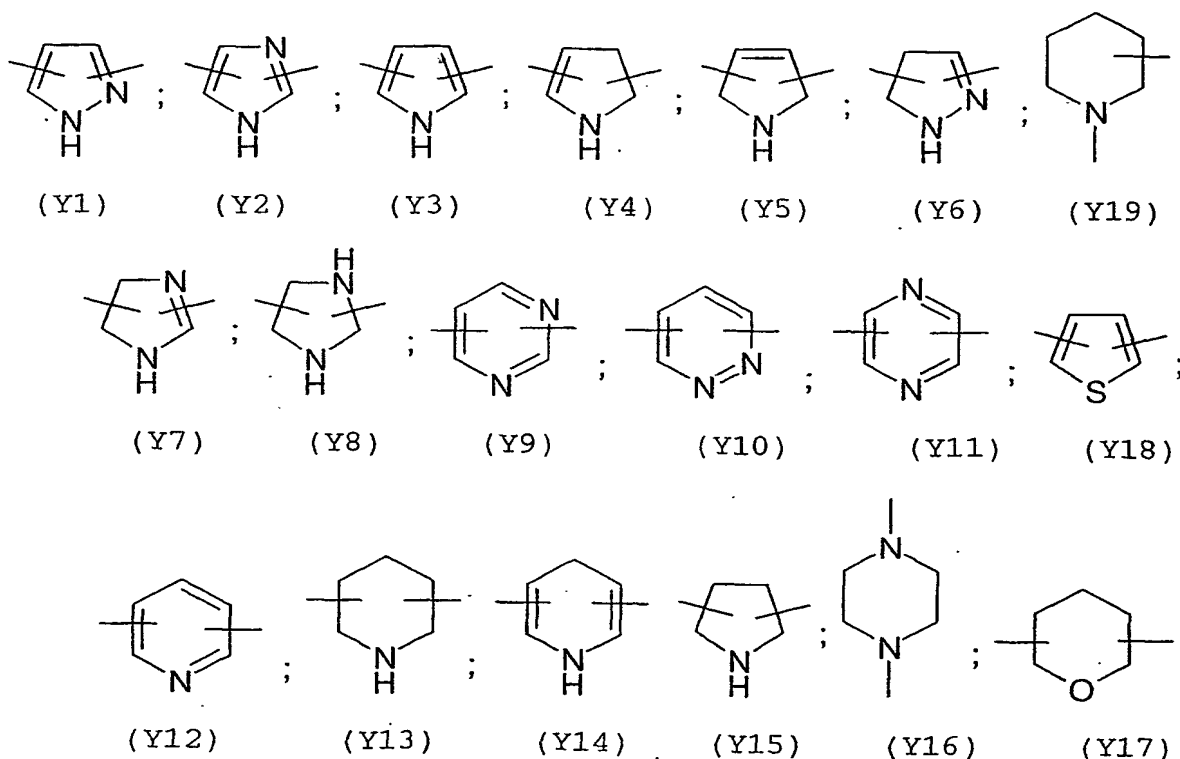
when in formula (II) $W = \text{C}$, $m = 2$ and $R_0 = -(\text{CH}_2)_n\text{-NH}_2$ with $n = 0$, $R_1 = \text{H}$, R_2 is the radical of formula (IIA) wherein $p = p_1 = p_2 = p_3 = 0$, R_4 and R_5 are free valences and between C_1 and C_2 there is one ethylene unsaturation, $Q = \text{H}$, in the radical A of formula (I) $T_1 = \text{CO}$ and the free valence of A is saturated with OH, the precursor drug of R is known as vigabatrin;

when in formula (II) $W = \text{C}$, $m = 0$ and $R_0 = -(\text{CH}_2)_n\text{-NH}_2$ with $n = 0$, $R_1 = \text{H}$, R_2 is the radical 3,4 di-hydroxy substituted benzyl, $T_1 = \text{CO}$ and the free valence of A is saturated with OH, the precursor drug of R is known as 2-amino-3-(3,4-dihydroxyphenyl)propanoic acid (dopa).

5. Compounds according to claims 1-2, wherein the precursors of $A = R\text{-}T_1$ in formula (I) are lamotrigine, topiramate, tiagabine, zonisamide, carbamazepine, felbamate,

amineptine, amoxapine, demexiptiline, desipramine, nortriptyline, opipramol, tianeptine.

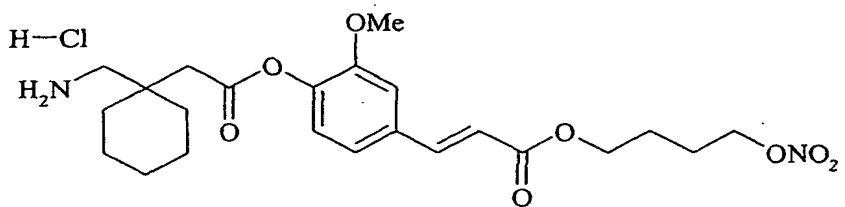
6. Compounds according to claims 1-5, wherein when in formula (I) $b_0 = 0$, Y in the bivalent linking group C is selected between Y_p and Y_{AR} as above defined.
7. Compounds according to claim 6, wherein Y^3 is selected from the following bivalent radicals:



8. Compounds according to claim 7, wherein Y^3 is selected from (Y12), having the two free valences in the ortho positions with respect to the nitrogen atom; (Y16) with the two valences linked to the two heteroatoms, Y1 (pyrazol) 3,5-disubstituted, (Y19) wherein the free valence on the ring is found in para position to the nitrogen atom.

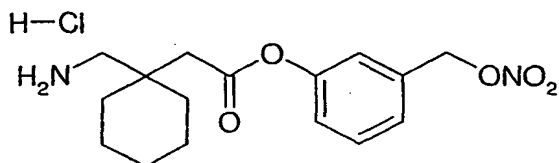
9. Compounds according to claims 1-8, wherein in formula (I) the precursors of B are the following: ferulic acid, N-acetylcysteine, cysteine, caffeic acid, hydro-caffeic and gentisic acid.
10. Compounds according to claims 1-9, wherein the precursor drugs are selected from gabapentine, norvaline, arginine, pregabalin, (S)3-isobutylGABA, agmatine.
11. Compounds according to claims 1-10, selected from the following:

1-(aminomethyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XV)



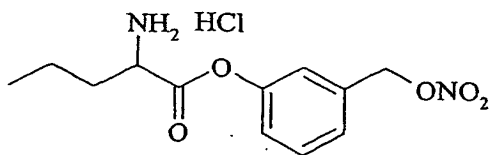
(XV)

1-(aminomethyl)cyclohexan acetic acid 3-(nitrooxymethyl) phenyl hydrochloride ester (XVI)



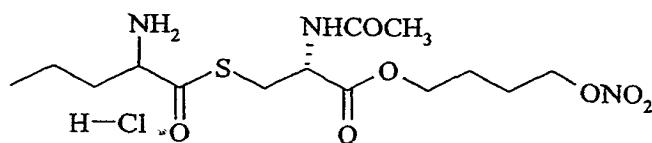
(XVI)

2-aminopentanoic acid 3-(nitrooxymethyl)phenyl hydrochloride ester (XVII)



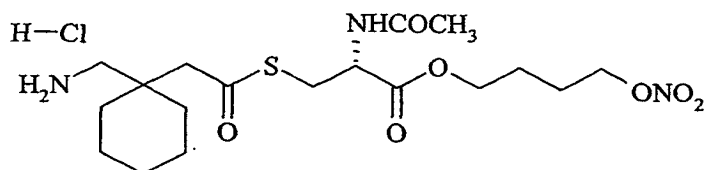
(XVII)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, 2-amino hydrochloride pentanoate (XVIII)



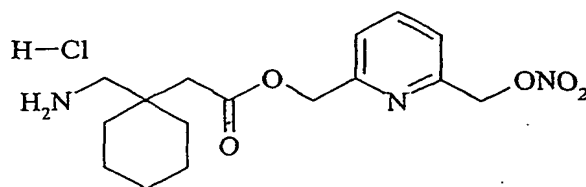
(XVIII)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, 1-(aminomethyl)cyclohexanacetate hydrochloride (XIX)



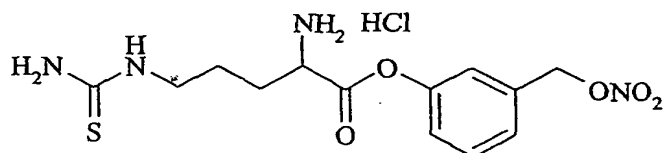
(XIX)

1-(aminomethyl)cyclohexanacetic acid-, [6-(nitrooxy methyl)-2-pyridinyl]methyl hydrochloride ester (XX)



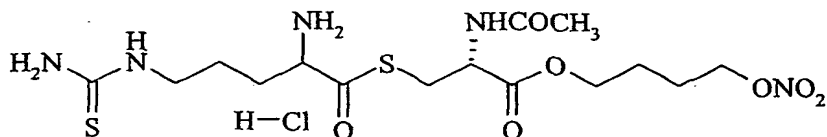
(XX)

alpha-amino-delta-thioureidopentanoic acid, 3-(nitrooxy methyl)phenyl hydrochloride ester (XXI)



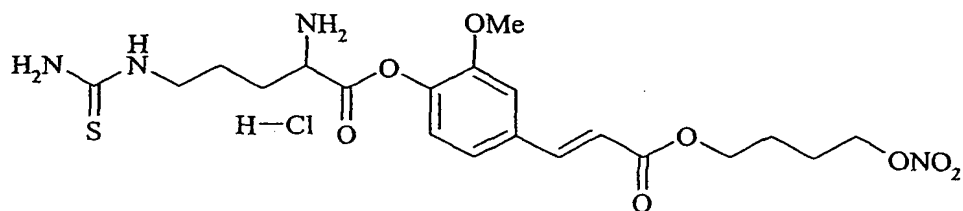
(XXI)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, alpha-amino-delta-thioureidopentanoate hydrochloride (XXII)



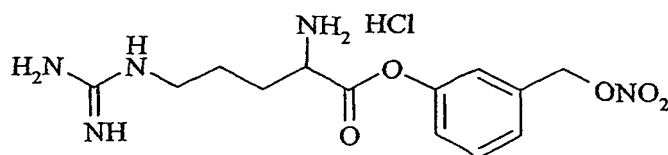
(XXII)

alpha-amino-delta-thioureidopentanoic acid, 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXIII)



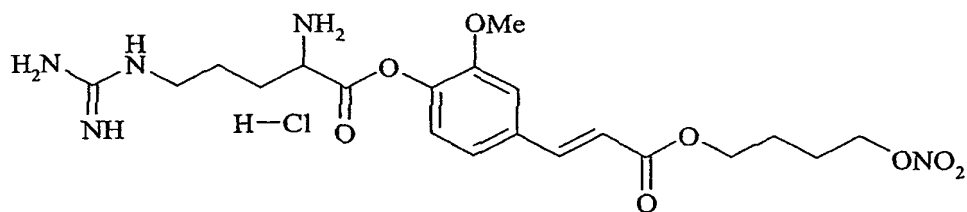
(XXIII)

2-amino-5-guanidinopentanoic acid, 3-(nitrooxy methyl)phenyl hydrochloride ester (XXIV)



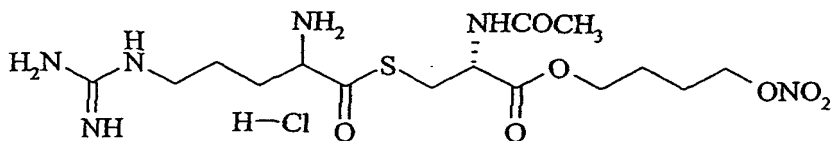
(XXIV)

2-amino-5-guanidinopentanoic acid-, 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXV)



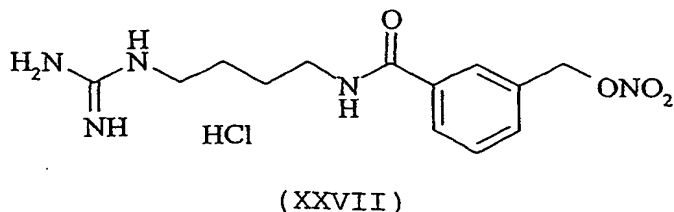
(XXV)

(S)-N-acetylcysteine-4-(nitrooxy)butyl ester, 2-amino-5-guanidinopentanoate hydrochloride (XXVI)

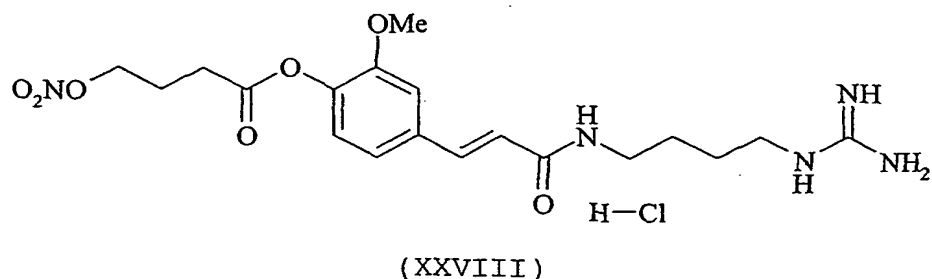


(XXVI)

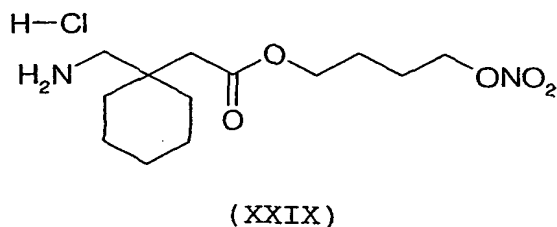
4-(guanidine)butyl-3-nitrooxymethylbenzamide
(XXVII)



4-(guanidine)butyl-3-[4-(4'-nitrooxybutyryloxy)-3-(methoxy)]phenyl-2-propenamide chloride (XXVIII)



1-(aminomethyl)cyclohexan acetic acid 4-(nitroxy)butyl hydrochloride ester (XXIX)



12. Compounds according to claims 1-11, as nitrate salts.
13. Compounds according to claims 1-12, in combination with NO-donor compounds.
14. Compounds according to claim 13, wherein the NO donor compounds contain in the molecule radicals of drugs belonging to the classes of aspirin, ibuprofen, paracetamol, naproxen, diclofenac, flurbiprofen.

15. Analgesic drugs for the treatment of the chronic pain, in particular the neuropathic pain, in combination with NO donor compounds.
16. Analgesic drugs according to claim 15, wherein the drug is selected from the following: lamotrigine, topiramate, tiagabine, zonisamide, carbamazepine, felbamate, amineptine, amoxapine, demexiptiline, desipramine, nortriptyline, opipramol, tianeptine, ami-triptyline, butriptyline, clomipramine, dibenzepin, dimetacrine, dothiepin, doxepin, fluacizine, imipramine, iprindole, lofepramine, melitracen, noxiptilin, propi-zepine, protriptyline, trimipramine.
17. Pharmaceutical compositions for parenteral, oral and topical use, comprising the compounds according to claims 1-16.
18. Compounds according to claims 1-17, for use as medicament.
19. Use of the compounds according to claims 1-17, for preparing drugs for the chronic pain, in particular the neuropathic pain.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 January 2003 (03.01.2003)

PCT

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A61K 31/21

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(25) Filing Language: English

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(81) Designated States (*national*): AE, AG, AL, AU, BA, BB,
BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE,
GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR,
LT, LV, MA, MG, MK, MN, MX, NO, NZ, OM, PH, PL,
RO, SG, SI, SK, TN, TR, TT, UA, US, UZ, VN, YU, ZA.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
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European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
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NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
27 March 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DRUGS FOR CHRONIC PAINS

(57) Abstract: Nitro-oxyderivative compounds or salts thereof having the following general formula (I): $A-(B)_{b0}-(C)_{c0}-NO_2$ wherein: $c0$ is an integer and is 0 or 1, $b0$ is an integer and is 0 or 1, $A = R-T_1$, wherein R is the radical of an analgesic drug for the chronic pain, in particular for the neuropathic pain; B is such that its precursor is selected from aminoacids, hydroxyacids, polyalcohols, compounds containing at least one acid function; C is a bivalent radical containing an aliphatic, heterocyclic or aromatic radical.



WO 03/000642 A3

INTERNATIONAL SEARCH REPORT

International Application No

Pⁱ EP 02/05166A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C203/04 A61K31/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No. 1
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X	WO 98 09948 A (NICOX SA ;DEL SOLDATO PIERO (IT); SANNICOLA FRANCESCO (IT)) 12 March 1998 (1998-03-12) page 45 -page 47 ---	1-14, 17-19
X	WO 00 44705 A (NICOX SA ;DEL SOLDATO PIERO (IT); GARUFI MICHELE (IT)) 3 August 2000 (2000-08-03) claims 1-5 --- -/--	1-14, 17-19

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

5 December 2002

Date of mailing of the international search report

11.12.02

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Authorized officer

Janus, S

INTERNATIONAL SEARCH REPORT

International Application No

P(P 02/05166

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 30866 A (NICOX SA ;ANTOGNAZZA PATRIZIA (IT); DEL SOLDATO PIERO (IT); BENEDI). 18 April 2002 (2002-04-18) claim 8 ---	1-14, 17-19
P,X	WO 02 30867 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 18 April 2002 (2002-04-18) claim 10 ---	1-14, 17-19
X	WO 96 19233 A (DEMOPULOS GREGORY A ;HERZ JEFFREY M (US); OMEROS MED SYS INC (US);) 27 June 1996 (1996-06-27) abstract ---	15,16
X	WO 00 06567 A (ALONSO ALIJA CRISTINA ;FUERSTNER CHANTAL (DE); STASCH JOHANNES PET) 10 February 2000 (2000-02-10) claim 17 ---	15,16
X	WO 00 54773 A (GARVEY DAVID S ;NITROMED INC (US)) 21 September 2000 (2000-09-21) page 14, line 11; claim 1 ---	15,16
X	WO 00 66582 A (ALONSO ALIJA CRISTINA ;STASCH JOHANNES PETER (DE); BAYER AG (DE);) 9 November 2000 (2000-11-09) claim 13 ---	15,16
P,X	WO 01 83490 A (ALONSO ALIJA CRISTINA ;STASCH JOHANNES PETER (DE); BAYER AG (DE);) 8 November 2001 (2001-11-08) claim 13 -----	15,16

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/05166

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-19 (all in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
no additional fees are to be refunded.

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-19 (all in part)

Present claims 1-14 relate to an extremely large number of possible compounds, of which only a very small number have actually been prepared, and only two (NO-gabapentin and NO-ASA) have been tested. This implies that the actual potential contribution of the application to the relevant art is the grafting of a 3-nitrooxymethyl-phenyl group to analgesic drugs and the possible change of activity profile linked therewith. Therefore, it is considered that support within the meaning of Article 6 PCT is to be found only for the above-mentioned part of the claimed scope.

In the present case, the claims so lack support that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims 1-14 which appear to be supported, namely those parts relating to the compounds of formula (I) wherein the group -T1-(B)b0-(C)c0-NO2 is a 3-nitrooxymethyl-phenyl group.

In addition, present claims 15 and 16 relate to products defined by reference to a desirable property, namely treatment of chronic pain and NO-donor. The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products listed in claim 16 insofar as the compounds for treatment of pain are concerned. The search on the NO-donor activity was based on a sample search.

Concerning claims 17-19, it has been noted that they mention the compounds of claims 1-16, 1-17 or 1-18, although only claims 1-14 relate to compounds. Only the part of claims 17-19 which relate to pharmaceutical compositions containing compounds belonging to the part of claims 1-14 which has been searched, the first and second medical indication thereof have been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-14, 17-19

Compounds of formula (I), pharmaceutical compositions containing them, their first and second medical indications.

2. Claims: 15, 16

Analgesic drugs for the treatment of chronic pain in combination with NO donor compounds.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

P EP 02/05166

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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